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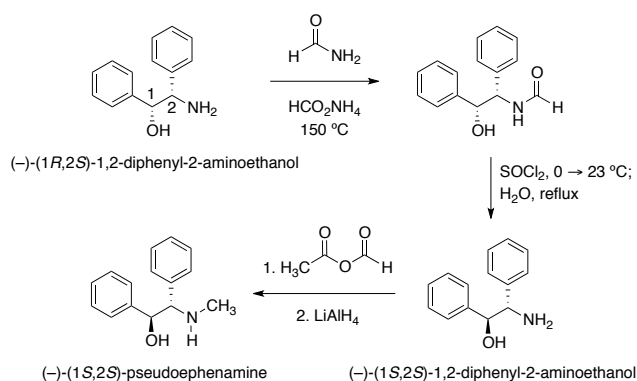
Pseudoephedrine: A Practical Chiral Auxiliary for Asymmetric Synthesis

Marvin R. Morales, Kevin T. Mellem, and Andrew G. Myers*

Pseudoephedrine is widely employed as a chiral auxiliary in diastereoselective alkylation reactions, providing ready access to enantiomerically enriched carboxylic acids, aldehydes, ketones, and alcohols.^[1] Because pseudoephedrine can be transformed into methamphetamine and other illegal drug substances, many countries restrict or ban its sale and distribution, which can complicate its use in industrial and academic settings.^[2] Here we report that (1*S*,2*S*)- and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol (synonymously, (1*S*,2*S*)- and (1*R*,2*R*)-pseudoephedrine,^[3] respectively) enable a broad range of utilities in asymmetric synthesis that meet or exceed those that previously characterized the pseudoephedrine system alone, with several advantages. Specifically, (1) these auxiliaries are free from regulatory restrictions and are not known to be transformable into illicit substances, (2) asymmetric alkylation reactions employing pseudoephedrine as a directing group proceed with equal or greater diastereoselectivities vis-à-vis the corresponding reactions employing pseudoephedrine, with notable improvements in the selectivities of alkylation reactions that form quaternary stereocenters, and (3) amides derived from pseudoephedrine exhibit a greater propensity to be crystalline substances relative to the corresponding pseudoephedrine derivatives and provide sharp, well-defined peaks in NMR spectra.

Both enantiomeric forms of pseudoephedrine are easily prepared using well-established methods (Scheme 1). In 1951, Tishler and co-workers at Merck reported a process for the transformation of *erythro*-1,2-diphenyl-2-aminoethanol (1*R*,2*S* or 1*S*,2*R*) into the corresponding *threo*-diastereomer (1*S*,2*S* or 1*R*,2*R*, respectively) by *N*-formylation with formamide, invertive cyclization to form the corresponding oxazoline using thionyl chloride, and hydrolytic ring-opening under acidic conditions.^[4,5] Employing a small but important modification (the use of formamide containing ~0.2 equiv ammonium formate for *N*-formylation rather than pure formamide, which leads to yellowing and a reduced yield of the product), we have applied the Tishler protocol for large-scale synthesis of both enantiomers of *threo*-1,2-diphenyl-2-aminoethanol from the appropriate *erythro*-diastereomer (both *erythro* diastereomers are commercially available in enantiomerically pure form and are widely used as chiral auxiliaries themselves, e.g., in the Williams amino acid synthesis).^[6–8]

Subsequent *N*-methylation of *threo*-1,2-diphenyl-2-aminoethanol was then achieved in 97% yield by *N*-formylation with acetic formic anhydride followed by reduction with lithium aluminum hydride.^[9] The product was recrystallized from hot ethanol to produce large, orthorhombic, colorless crystals (mp 109–110 °C).^[10] We have routinely prepared 20–40-g batches of (1*R*,2*R*)- or (1*S*,2*S*)-pseudoephedrine by the 4-step sequence described, which proceeds in 87% yield and requires no column chromatography.^[11,12] X-ray crystallographic analysis revealed that pseudoephedrine adopts a conformation identical to pseudoephedrine in the solid state, with gauche orientations between both the aminomethyl and hydroxyl substituents as well as the two phenyl substituents (Figure 1).



Scheme 1. Synthesis of (–)-(1*S*,2*S*)-pseudoephedrine by a modified Tishler protocol followed by *N*-methylation.

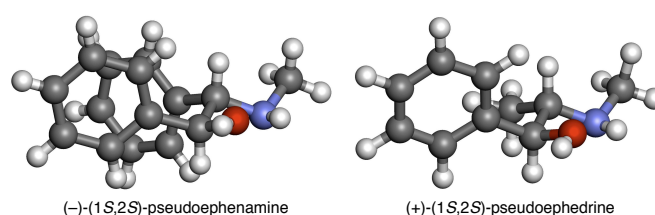


Figure 1. X-ray crystal structures of (–)-(1*S*,2*S*)-pseudoephedrine and (+)-(1*S*,2*S*)-pseudoephedrine.^[13]

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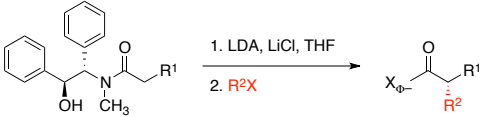
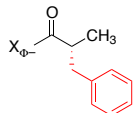
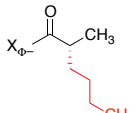
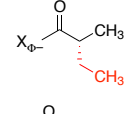
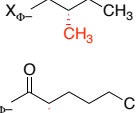
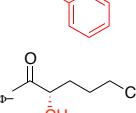
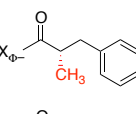
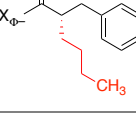
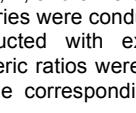
[**] We gratefully acknowledge the NSF (CHE-0749566) and the NIH (CA-047148) for financial support of this research. We also wish to thank Dr. Shao-Liang Zheng for X-ray crystallographic analyses and Dr. David Kummer for helpful discussions.



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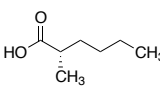
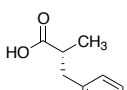
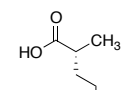
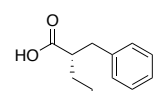
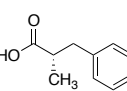
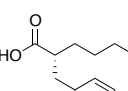
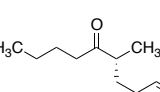
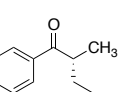
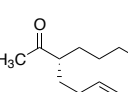
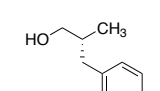
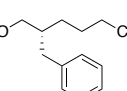
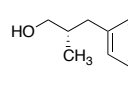
Amide derivatives of pseudoephedrine were prepared from the corresponding carboxylic acid chlorides or anhydrides by routine methods and, in most cases, were crystalline solids (see Supporting Information). Pseudoephedrine amide enolates were generated with lithium diisopropylamide (2.2 equiv) in tetrahydrofuran (THF) at –78 °C in the presence of a saturating amount of anhydrous lithium chloride (ca. 6 equiv), conditions identical to those employed for enolization of pseudoephedrine amides.^[1e] Pseudoephedrine propionamide was poorly soluble in THF alone, precluding the use of this solvent for enolization; a 1:1 mixture of THF-pyridine proved to be a viable reaction solvent for generation

Table 1. Diastereoselective Alkylation of Pseudoephedrine Amides.

					
Entry ^[a]	Product	Crude dr ^[b]	Isolated dr ^[b]	Yield (%)	mp (°C)
1		95:5	≥99:1	85	128–129
2		95:5	98:2	97	NA
3		≥94:6	98:2	96	NA
4		≥96:4	≥99:1	87	89–90
5		≥98:2	≥99:1	99	112–114
6		95:5	98:2	84	77–79
7		98:2	98:2	92	NA
8		≥99:1	≥99:1	99	109–111

[a] Entries 1, 2, and 3 were conducted in 1:1 THF-pyridine as solvent; all other entries were conducted in THF alone as solvent. All reactions were conducted with excess alkyl halide (1.5–4.0 equiv). [b] Diastereomeric ratios (dr) of isolated products ranged from 98:2 to ≥99:1; crude dr values are listed in Table 1]. Reaction diastereoselectivities were initially measured by direct HPLC analysis of the products, but we later determined that they were also readily assessed by ¹H NMR analysis of the corresponding oxazolinium triflate derivatives, obtained by invertive cyclization with triflic anhydride (see Supporting Information for details).^[14] Diastereoselectivities were uniformly high, as in the corresponding alkylation reactions of pseudoephedrine amides. The majority of the alkylation products were solids.

Chart 1. Transformations of Pseudoephedrine Amides into Enantiomerically Enriched Carboxylic Acids, Alcohols, and Ketones.

Carboxylic Acids (via acidic or basic hydrolysis): ^[a]		
		
93%, 95% ee 97%, ≥95% ee	98%, 98% ee 99%, 95% ee	89%, 92% ee 94%, 91% ee
		
93%, ≥97% ee	99%, 92% ee	98%, 90% ee
Ketones (via aryl or alkyllithium addition):		
		
95%, ≥95% ee	96%, ≥93% ee	98%, ≥95% ee
Alcohols (via LAB reduction):		
		
91%, 98% ee	89%, 95% ee	94%, 87% ee

[a] Acidic hydrolysis was achieved by heating the amide to 115 °C with 9 N sulfuric acid in dioxane. Basic hydrolysis was achieved by heating the amide to 95 °C with tetrabutylammonium hydroxide in a 3:1 mixture of *tert*-butyl alcohol and water.^[1e]

Optically active carboxylic acids, ketones, and alcohols were obtained directly from alkylated pseudoephedrine amides using methods paralleling those previously employed for similar transformations of pseudoephedrine amides (Chart 1). Thus, hydrolysis of pseudoephedrine amides under both acidic and basic conditions provided carboxylic acids in high yields with little or no epimerization of the α -carbon center (89–99% yield), addition of organolithium reagents to pseudoephedrine amides afforded enantiomerically enriched ketones (95–98% yield), and reduction of pseudoephedrine amides with lithium amidotrihydroborate (LAB)^[15] gave the corresponding primary alcohols (89–94% yield).^[1e] Preliminary experiments exploring the direct transformation of pseudoephedrine amides to aldehydes using lithium triethoxyaluminum hydride as reductant have not yet provided high yields of product (~30–60%).

Table 2. Quaternary Carbon Centers Formed by Enolization–Alkylation of α,α -Disubstituted Pseudoephedrine Amides.

Entry	Product	Yield (%)	dr ^[a]
1		85	$\geq 19:1$ ($\geq 19:1$)
2		99	$\geq 19:1$ (14:1)
3		91	$\geq 19:1$ (7.3:1)
4		87	$\geq 19:1$ (8.3:1)
5		82	$\geq 19:1$ ($\geq 19:1$)
6		80	9.9:1 ^[b] (6.2:1)

[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine. [b] The product diastereomers were separated using radial chromatography. The major diastereomer was isolated in 71% yield ($\geq 19:1$ dr), and the minor diastereomer was isolated in 6% yield ($\geq 19:1$ dr).

Two methods for the alkylative construction of quaternary carbon centers using pseudoephedrine as a chiral auxiliary were investigated, and, in both cases, significant enhancements in diastereoselectivities were observed compared to the corresponding transformations using pseudoephedrine. The first method involved sequential enolization-alkylation of α,α -disubstituted pseudoephedrine amides (Table 2), while the second method used a conjugate addition-alkylation protocol^[16] with α -alkyl- α,β -unsaturated pseudoephedrine amides (Table 3).^[17] In nearly all of the alkylation reactions, the ¹H NMR spectra of the crude reaction products were exceptionally clean and, indeed, in many cases the unpurified products appeared to be diastereomerically pure. The ¹H NMR spectra were further simplified by the fact that the products appeared to exist in a single rotameric form; X-ray crystallographic analysis of the product of Entry 1 (Table 2) revealed that, in the solid state, this substance adopts the rotameric form in which the *N*-methyl group is *cis* to the quaternary center, and we believe that this is likely the case in solution as well. We confirmed that the isolated products were formed with $\geq 19:1$ dr by ¹H NMR analysis of the corresponding oxazolinium triflate derivatives, formed with triflic anhydride. Only the example of Entry 6 (Table 2) proceeded with a diastereomeric ratio $< 19:1$ (dr 9.9:1), and, in this instance, the

Table 3. Quaternary Carbon Centers Formed by Conjugate Addition-Alkylation of α,β -Unsaturated Pseudoephedrine Amides.

Entry	Product	Yield (%)	dr ^[a]
1		75	$\geq 19:1$ (10.1:1)
2		77	$\geq 19:1$ (11.1:1)
3		80	$\geq 19:1$ ($\geq 19:1$)
4		85	$\geq 19:1$ (12.5:1)
5		79	$\geq 19:1$ (9.1:1)
6		76	$\geq 19:1$ (8.2:1)

[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine.

diastereomers could be separated by radial chromatography (facilitated by the UV activity of the auxiliary). As with the α,α -disubstituted amide products, the majority of α -quaternary amide products are solids, whereas pseudoephedrine α -quaternary amide products are typically oils.

Our findings suggest that, in many ways, pseudoephedrine is a superior chiral auxiliary for asymmetric synthesis when compared to pseudoephedrine. Advantages include the fact that pseudoephedrine is free of regulatory restrictions, that pseudoephedrine amides have physical properties that facilitate their physical processing and spectroscopic analysis (greater crystallinity, lack of line-broadening in NMR spectra), and that alkylation reactions that form amide products with α -quaternary carbon centers proceed with notably higher diastereoselectivities.^[18] Although pseudoephedrine is not commercially available at this time, so far as we are aware, it is easily synthesized in large amounts from starting materials that are available in bulk at very low cost.

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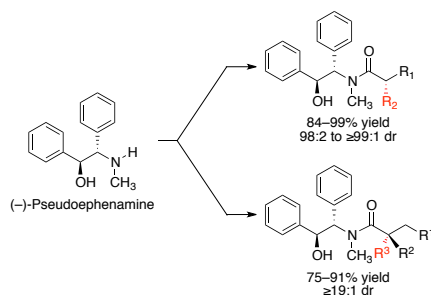
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Pseudoephedrine: A Practical Chiral
Auxiliary for Asymmetric Synthesis



Pseudoephedrine is shown to be a versatile chiral auxiliary for asymmetric synthesis. It is free from regulatory restrictions and exhibits remarkable stereocontrol in alkylation reactions, especially those that form quaternary carbon centers. Amides derived from pseudoephedrine exhibit a high propensity to be crystalline substances and provide sharp, well-defined peaks in NMR spectra.